This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 21!

See attached form for additional information.

Interagency Report Control No.: 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

1. **CERTIFICATE NUMBER:** 51-F-0016
CUSTOMER NUMBER: 441

FORM APPROVED
OMB NO. 0579-0036

National Institutes of Health
31 Center Drive, Room B1C37
Bethesda, MD 20891

Telephone: (301) -496-5424

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Atached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY **(Attach additional sheets if necessary or use APHIS Form 7023A)**

A. **Animals Covered By The Animal Welfare Regulations**	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report).	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs	7	67	114		181
5. Cats	13	4			4
6. Guinea Pigs	69	563	22	12	597
7. Hamsters	2634	53	707	4	764
8. Rabbits	128	446	495		941
9. Non-human Primates	1227	1663	579	17	2259
10. Sheep		27			27
11. Pigs	38	75	157		232
12. Other Farm Animals					
Cattle		2			2
13. Other Animals					
Chickens	1560	2			2
Turkey		1			1
Gerbils		6			6

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anestetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)
ify that the above is true, correct, and complete (7 U.S.C. Section 2143)

(b)(6), (6)(7)(C)

SI

NAME & TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL *(Type or Print)*

(b)(6), (6)(7)(C)

DATE SIGNED: 11/23/08

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This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

See reverse side for additional information.

Interagency Report Control No
0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

CONTINUATION SHEET FOR ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

1. REGISTRATION NO. 51-F-0016
CUSTOMER NO. 441

FORM APPROVED
OMB NO. 0579-0036

2. HEADQUARTERS RESEARCH FACILITY *(Name and Address, as registered with USDA, include Zip Code)*
National Institutes of Health
31 Center Drive (b)(2)High, (b)(7)(E)
Bethesda, MD 20892

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets if necessary or use this form.)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report)*	F. TOTAL NO. OF ANIMALS **(Cols. C + D + E)**
Ferrets		58	14	20	92
Ground Squirrels	126	95			95
Wild Mice	263	44			44
Llama		1			1

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all the exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional official)
(b)(6), (6)(7)(C)
ve is true, correct, and complete (7 U.S.C. Section 2143)

SIGN

NAME & TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL *(Type or Print)*
Michael M. Gottesman, M.D.
(b)(6), (6)(7)(C)

DATE SIGNED
11/23/08

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PART 1 - HEADQUARTERS

NOV 26 2008

EXPLANATION FOR COLUMN E LISTING

This form is intended as an aid to completing the USDA Annual Report of NIAID Research Facilities Column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: **51-F-0016**
2. Number of animals used under Column E conditions in this study: **12**
3. Species (common name) of animals used in this study: **Guinea pig**
4. Explain the procedure producing pain and/or distress, including reason (s) for species selected.

   It is essential to study anti-HSV-2 drugs and HSV-2 candidate vaccines in animal models before clinical testing in humans. The guinea pig is chosen because HSV-2 infection of guinea pigs causes mucocutaneous lesions as found in man. There are seven possible routes of infection used to study herpes simplex virus pathogenesis in animal models. We used the vaginal route for HSV-2 since we are interested in developing vaccines that can protect humans from genital infection by HSV-2.

   Wild-type HSV infection of guinea pigs causes mucocutaneous lesions, ulcers, and may cause hind-limb paralysis or death in some animals. To determine if the vaccine candidates can prevent or reduce disease caused by wild-type virus, guinea pigs were inoculated with vaccine candidates and later challenged with wild-type virus at a dose that can cause disease. We allowed the infection to progress to moribundity so that we can measure the severity of primary disease and the rate of reactivation of HSV over time.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine (personal experience or literature search) that pain and/or distress relief would interfere with test results.

   The animals did not receive pain-relieving medicines, such as NSAIDS, because they alter the immune response and therefore interferes with the outcome and interpretation of experimental results. Opioids were not administered because they interfere with virus reactivation (a measured outcome) by interacting with receptors on the surface of neurons where the virus is maintained during latency.

Information below will NOT be forwarded to USDA as part of the Annual Report

NOV 2 6 2008

EXPLANATION FOR COLUMN E LISTING

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1. Registration Number: **51-F-0016**
2. Number of animals used under Column E conditions in this study: **4**
3. Species (common name) of animals used in this study: **Hamster**
4. Explain the procedure producing pain and/or distress, including reason (s) for species selected.

   Leishmanial diseases are major parasitic diseases of man. The stage of the parasite that grows in the vertebrate host and causes disease cannot be generated *in vitro*. It can only be obtained from *in vivo* sources hence the whole animal is required to study experimental vaccines, protective immune responses and the outcome of infection of vaccinated animals.
   The hamster is the only laboratory animal that develops visceral leishmaniasis. Hepatomegaly and anemia are manifestations of the disease. The progression of visceral infection in hamsters is not associated with any overt pathology or changes in behavior until the infection is severe. Onset of symptoms occurred 12 - 16 weeks post infection with infected animals displaying symptoms of cachexia and morbidity.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine (personal experience or literature search) that pain and/or distress relief would interfere with test results.

   Analgesics were not used during the two-day period after morbidity because they affect endpoint organ size, histology, and parasite load. Euthanasia was the only means to relieve pain and distress.

Information below will NOT be forwarded to USDA as part of the Annual Report

NOV 2 6 2008

EXPLANATION FOR COLUMN E LISTING

This form is intended as an aid to completing the column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: **51-F-0016**
2. Number of animals used under Column E conditions in this study: 7
3. Species (common name) of animals used in this study **Cynomolgous monkeys**
4. Explain the procedure producing pain and/or distress, including reason (s) for species selected.
   The cynomolgus monkey was chosen because it is more susceptible than the rhesus and African green monkey to monkeypox infection. All of the animals developed febrile and pustular disease, dyspnea, and recumbency. It was necessary to allow the clinical course of monkey pox (MPOX) infection to progress to this level so the appropriate lethal dose (minimum 100% mortality) could be determined.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.

The animals exposed to MPOX were not treated with analgesics (NSAIDS and opioids) because each has a profound effect on the immune system (cytokine/chemokine levels, interferon levels, and markers of leukocyte activation) and would alter data. Opiods were also contraindicated because they cause histamine release and respiratory depression.

Information below will NOT be forwarded to USDA as part of the Annual Report

NOV 2 6 2008

EXPLANATION FOR COLUMN E LISTING

This form is intended as an aid to completing the column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: **51-F-0016**
2. Number of animals used under Column E conditions in this study: **6**
3. Species (common name) of animals used in this study **Cynomolgous monkeys**
4. Explain the procedure producing pain and/or distress, including reason (s) for species selected.

The Old World monkeys were chosen for this study because they are a well-studied species for pox virus infections. The animals were infected with Cowpox Virus (CPOX) to identify and develop an appropriate non-human primate model system for smallpox (SPOX) infections in man. To determine the minimum 100% mortality dose of this virus, it was necessary to allow the clinical course of CPOX infection to progress to a stage of significant morbidity to gain increased statistical confidence that the appropriate lethal dose was properly determined.

Some of the pain/ discomfort these animals experienced was fever, muscle pain, labored breathing and skin blisters. The symptoms were a result of the virus destroying body tissue and the animal's immune response. Survival is a FDA parameter therefore proof of protection is a necessary step towards the approval of vaccines and therapeutics intended for human use. All animals were humanely euthanized when survival was not deemed probable.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.

The animals exposed to CPOX were not treated with analgesics (NSAIDS and opioids) because each have a profound effect on the immune system (cytokine/chemokine levels, interferon levels, and markers of leukocyte activation) and would alter data. Opiods were also contraindicated because they cause histamine release and respiratory depression.

Information below will NOT be forwarded to USDA as part of the Annual Report

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Column E Explanation Form

This form is intended as an aid to completing the Column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by laypersons as well as scientists.

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1. Registration Number: 51-F-0016

2. Number of animals used under Column E conditions in this study: 4

3. Species (common name) of animals used in this study: *Macaca mulatta*

One of the aims of our on going studies of early differential rearing experiences and pharmacological treatment strategies is to examine the impact of these experiences on sensitivity to depressogenic and anxiogenic challenges. *The behavioral, physiological, and immunological similarities between humans and monkeys make monkeys ideal for this study. Moreover their long sleep/wake architecture emulates that of man (non-nocturnal and well-defined with long circadian and ultraradian rhythms) and allows a direct comparison to the sleep changes seen in the clinical population treated with IFN-alpha and associated with depressive syndromes. The monkey brain has a well-developed temporal lobe and an extensive prefrontal cortex, regions that are largely undeveloped in the rodent. These areas, which may be important for disturbances in human psychopathology, can be studied with invasive in vivo imaging and ex vivo techniques in monkeys.*

4. Explain the procedure producing pain and/or distress, including reason(s) for species selected.

Chronic immune activation induced by treatment with the cytokine IFN-alpha may cause a behavioral syndrome in the monkeys similar to that of depression in humans. This behavioral syndrome may include blunted motivation, apathy, and sleepiness. In addition to this behavioral state, animals may experience heightened pain sensitivity and somatic and neurological symptoms. Pain or distress relieving measures will not be used in this study except as they relate to the reduction of pain and distress secondary CSF sampling and PET/MRI imaging.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.

The depressive syndrome elicited by IFN-alpha is the phenomenon under study. Relief of the associated symptoms would likely alter the underlying mechanisms which we seek to examine. At the present time there are very few validated models of depressive syndrome in monkeys and even fewer related to depressogenic effects of interferon-alpha.

A Nov 11, 2007 review of 216 citations yielded by a search of PUBMED and PSYCHINFO with the following keywords ((affective disorder or antidepressant or depressogenic or interferon alpha) and (monkey or monkeys)) did not provide suitable alternatives to address the goals of this examination.

Information below will NOT be forwarded to USDA as part of the Annual Report.

NOV 2 6 2008

EXPLANATION FOR COLUMN E LISTING

This form is intended as an aid to completing the USDA Annual Report of NIAID Research Facilities Column E explanation. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: **51-F-0016**
2. Number of animals used under Column E conditions in this study: **20**

3. Species (common name) of animals used in this study: **Ferrets**
4. Explain the procedure producing pain and/or distress, including reason (s) for species selected.

This project is to understand the pathogenesis of pandemic/potentially pandemic strains of influenza A virus. Viral infection and induction of an inflammatory response can only be studied in living animals. Ferrets are a well-established model for studying the pathogenesis of influenza virus infections. Ferrets infections resulted in symptoms ranging from mild disease to severe pneumonia. In this regard the progression resembled the 1918 and H5N1 pandemic influenza infections in man.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine (personal experience or literature search) that pain and/or distress relief would interfere with test results.

Antiviral drugs or antipyretics/analgesics were not administered to animals that displayed clinical signs because they interfere with the pathogenesis of the disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) were not administered to ferrets exhibiting a febrile response because that response is an important endpoint for validating this model of human pandemic influenza virus infections. NSAIDS were also contraindicated because they interfere with the inflammatory response which affects the course of the disease.

Information below will NOT be forwarded to USDA as part of the Annual Report

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